ClinicalEvidence

Diabetes: glycaemic control in type 1

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ABSTRACT

INTRODUCTION: Type 1 diabetes occurs when destruction of the pancreatic islet beta cells, usually attributable to an autoimmune process, causes the pancreas to produces too little insulin or none at all. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of intensive treatment programmes and educational interventions in adults and adolescents with type 1 diabetes? What are the effects of different insulin regimens on glycaemic control in adults and adolescents with type 1 diabetes? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2006 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 16 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: different frequencies of insulin administration (continuous subcutaneous insulin infusion compared with multiple daily subcutaneous insulin injections); different frequencies of blood glucose self-monitoring; educational interventions; and intensive treatment programmes.

QUESTIONS

INTERVENTIONS

INTENSIVE TREATMENT PROGRAMMES AND EDUCATIONAL INTERVENTIONS

Likely to be beneficial

INSULIN REGIMENS

Trade off between benefits and harms

Unknown effectiveness

Covered elsewhere in Clinical Evidence

Diabetes: prevention of cardiovascular events

To be covered in future updates

Different types of insulin compared with each other

Key points

- Type 1 diabetes occurs when destruction of the pancreatic islet beta cells, usually attributable to an autoimmune process, causes the pancreas to produces too little insulin or none at all.

  The prevalence of type 1 diabetes is 0.02% in people aged 0–14 years, and it is estimated that 430,000 people in this age group have type 1 diabetes worldwide.

  Although type 1 diabetes usually accounts for only a minority of the total burden of diabetes in a population, it is the predominant form of the disease in younger age groups in most resource-rich countries.

- Glycaemic control typically worsens in adolescence, owing to a combination of physical and psychological change and development.

- There is some evidence that educational and psychosocial interventions may improve glycaemic control and quality of life in adults and adolescents with type 1 diabetes.

- Intensive treatment programmes in adults seem to improve glycaemic control compared with conventional treatment, and they have potential benefits over the long term; but they require significant investment of time and resources. Data in adolescents are lacking.

  Better glycaemic control is associated with higher rates of hypoglycaemia, which may not be acceptable to some people with type 1 diabetes.

- While regular self-monitoring of blood glucose is recommended to adults with type 1 diabetes, outside the setting of intensive and structured insulin-management programmes, such as DAFNE (Dose Adjustment for Normal Eating training), there are no reliable data on which to base advice about optimum frequency of blood glucose self-testing.

- Continuous subcutaneous insulin infusion seems effective at improving glycated haemoglobin levels and quality of life compared with multiple daily subcutaneous injections.

  However, continuous subcutaneous insulin infusion is associated with an increased risk of diabetic ketoacidosis due to disconnection or malfunction of the pump, and to infection.

DEFINITION   The term diabetes mellitus encompasses a group of disorders characterised by chronic hypergly-caemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects of insulin secretion, insulin action, or both. The WHO definition now recognises diabetes as a progressive disorder of glucose metabolism in which individuals may move between normoglycaemia, impaired glucose tolerance or impaired fasting glycaemia, and frank hyperglycaemia. Type 1 diabetes occurs when destruction of the pancreatic islet beta cells, usually attributable to an autoimmune process, causes the pancreas to produces too little insulin or none at all. Markers of autoimmune destruction (autoantibodies to islet cells, autoantibodies to insulin, or autoantibodies to both islet cells and insulin, and to glutamic acid decarboxylase) can be found in 85–90% of people with type 1 diabetes when hyperglycaemia is first detected. [1] The definition of type 1 diabetes also includes beta cell destruction, in people prone to ketoacidosis, for which no specific cause can be found. However, it excludes those forms of beta cell destruction for which a specific cause can be found (e.g. cystic fibrosis, pancreatitis, pancreatic cancer). [2] Type 2 diabetes results from defects in both insulin secretion and insulin action. Type 2 diabetes is not covered in this review. **Diagnosis:** In the presence of symptoms (such as thirst, passing increased volumes of urine, blurring of vision, and weight loss), diabetes may be diagnosed on the basis of a single random elevated plasma glucose (at least 11.1 mmol/L). In the absence of symptoms, the diagnosis should be based on at least one additional blood glucose result in the diabetes range, either from a random or fasting (plasma blood glucose at least 7.0 mmol/L) sample, or from the oral glucose tolerance test (plasma blood glucose (at least 11.1 mmol/L 2 hours after a 75 g glucose load). [2] **Population:** For the purpose of this review, we have included adolescents and adults with type 1 diabetes, but have excluded pregnant women and people who are acutely unwell: for example, after surgery or MI.

INCIDENCE/ PREVALENCE   The prevalence of type 1 diabetes is 0.02% in people aged 0–14 years, and it is estimated that 430,000 people in this age group have type 1 diabetes worldwide, with annual increase in incidence of 3%. [3] Each year, 65,000 new cases are diagnosed in this age group. Although type 1 diabetes usually accounts for only a minority of the total burden of diabetes in a population, in most resource-rich countries it is the predominant form of the disease in younger age groups. About a quarter of people with diabetes come from the South-East Asian region, and a fifth from the European region. [3] Studies have suggested that age of incidence is shifting to a younger age group. [4] This younger age at onset means that complications appear at a younger age, and dependence on lifelong insulin imposes a heavy burden on health services. The prevalence of diabetes (including both type 1 and 2) in the United Kingdom is estimated to be 3.54%, totalling 2.2 million people.

AETIOLOGY/ RISK FACTORS   Two main aetiological forms of type 1 diabetes are recognised. Autoimmune diabetes mellitus results from autoimmune-mediated destruction of the beta cells of the pancreas. The rate of destruction varies, but all people with this form of diabetes eventually become dependent on insulin for survival. Peak incidence of autoimmune diabetes is during childhood and adolescence, but it may occur at any age. There is a genetic predisposition, and people with this type of diabetes may have other autoimmune disorders. [5] Certain viruses, including rubella, Coxsackie B, and cytomegalovirus, have been associated with beta cell destruction. Other environmental factors are probably also contributory, but these are poorly defined and understood. Idiopathic diabetes (in which the cause is unidentified) is more common in individuals of African and Asian origin. [2]

PROGNOSIS   Untreated, most people with type 1 diabetes, particularly those with autoimmune diabetes mellitus, will experience increasing blood glucose levels, progressing to ketoacidosis resulting in coma and death. The course of idiopathic diabetes may be more varied, with some people experiencing permanent lack of insulin and a tendency to ketoacidosis, although in others the requirement for insulin treatment may fluctuate. [2] However, most people with type 1 diabetes require insulin for survival, and are described as insulin dependent. The long-term effects of diabetes include retinopathy, nephropathy, and neuropathy. People with diabetes mellitus are also at increased risk of CVD, PVD, and cerebrovascular disease. Good glycaemic control can reduce the risk of developing diabetes-related complications. [6]

AIMS OF INTERVENTION   To control blood glucose levels; to maximise quality of life; to prevent diabetes-related emergencies, such as ketoacidosis; to maintain HbA1c levels at optimal level in order to slow disease progression and to reduce risk of micro- and macrovascular complications; to minimise adverse effects of treatment.

OUTCOMES	**Primary outcomes:** Change in glycated haemoglobin (measured as HbA1c); quality of life; incidence of and mortality from hypoglycaemia; incidence of and mortality from diabetic ketoacidosis; weight gain; fluid retention; neuropsychological impairment; adverse effects. **Secondary outcomes:** all-cause mortality; other long-term outcomes, such as development of retinopathy, nephropathy, neuropathy, and CVD.
METHODS	*BMJ Clinical Evidence* search and appraisal December 2006. The following databases were used to identify studies for this systematic review: Medline 1966 to December 2006, Embase 1980 to December 2006, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2006, Issue 4. Additional searches used these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. Studies for inclusion were identified by an initial search for systematic reviews and meta-analyses. Where a good-quality systematic review was available, a further search was done for RCTs from the date of the review only. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in the English language. RCTs had to be assessor-blinded — studies described as "open", "open label", or not blinded were excluded unless blinding was impossible. RCTs had to contain 20 or more individuals, of whom 80% or more were followed up. There was no minimum length of follow-up required to include studies, apart from for HbA1c levels, where 3-month follow-up was required. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. Measuring glycated haemoglobin using HbA1c is now the standard method for monitoring glycaemic control. Therefore, studies using measures of glycaemic control other than HbA1c have only been included where studies using HbA1c as a measure for glycated haemoglobin are unlikely to be conducted. Crossover trials were included only if results were reported at the end of the initial treatment period before crossover. Reference lists were searched for further systematic reviews or RCTs not identified by the initial search. Educational interventions are defined as interventions, single, or multiple, that provide information, self-management programmes, or both. Interventions primarily focused on the organisational aspects of delivery of care have been excluded. Educational interventions for adults and adolescents have been considered separately, as adolescents are generally acknowledged to have different educational needs from adults, and poorer glycaemic control. Studies testing the effects of multiple-intervention programmes without an education component have been excluded. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 12).

QUESTION **What are the effects of intensive treatment programmes and educational interventions in adults and adolescents with type 1 diabetes?**

OPTION **INTENSIVE TREATMENT PROGRAMMES**

Glycaemic control
Compared with conventional treatment programmes or control Intensive treatment programmes may be more effective at reducing glycated haemoglobin levels (measured as HbA1c levels) at 1–10 years in adults (very low-quality evidence).

Quality of life
Compared with conventional treatment programmes or control Intensive treatment programmes and conventional treatment programmes seem equally effective at improving diabetes-dependent quality of life in adults (moderate-quality evidence).

Mortality
Compared with conventional treatment programmes or control Intensive treatment programmes do not increase all-cause mortality in adults, but are more likely to increase mortality that is potentially associated with acute complications of intensive treatment (moderate-quality evidence).

Adverse effects
Compared with conventional treatment programmes or control Intensive treatment programmes are more likely to increase the risk of hypoglycaemia, diabetic ketoacidosis (when the treatment programme involves the use of insulin pumps), and weight gain in adults (moderate-quality evidence).

Note
We found no clinically important results about intensive treatment programmes compared with conventional treatment programmes or control for clinical outcomes of interest specifically in adolescents.

For GRADE evaluation of interventions for diabetes: glycaemic control in type 1, see table, p 12 .

Benefits:

Adults:

We found one systematic review (search date 2002), [7] and one additional RCT in two reports. [6] [8] The systematic review identified one RCT comparing intensive treatment programmes versus control treatment. [9] People in the intensive treatment programme were recommended multiple insulin injections and frequent blood glucose monitoring, with goals for home blood glucose levels set individually, and an overall target HbA1c of 7%. Telephone contact was made every 2 weeks, or more frequently initially if needed, with review in the clinic every 2 months. People in the control group were advised to monitor their blood glucose and adjust their insulin to achieve lower blood glucose levels; the goal of treatment was to reduce blood glucose without giving rise to serious hypoglycaemia. The RCT identified by the review found that, compared with control treatment, intensive treatment programmes significantly reduced HbA1c levels at 1.5, 3.0, 5.0, 7.5, and 10.0 years (102 people, mean age 31 ± 7.4 years, attending an outpatient clinic; mean reduction in HbA1c v controls: 1.5% at 1.5 years, figures extrapolated from graph, no standard error of the mean given; 1.6 ± 0.1% at 3.0 years; 1.5 ± 0.1% at 5.0 years; 1.4 ± 0.7% at 7.5 years; 1.1 ± 0.6% at 10.0 years; P less than 0.01 for all outcomes). [9] In the additional RCT, the intensive treatment programme consisted of multiple daily injections of insulin or continuous subcutaneous insulin infusion, with the dosage adjusted according to the results of blood glucose self-monitoring done at least four times daily, dietary intake, and anticipated exercise, in order to meet preset blood glucose targets. Conventional treatment consisted of one or two subcutaneous insulin injections daily, daily self-monitoring of urine or blood glucose, and education about diet and exercise. People in the intensive treatment programme were seen at the study centre every month, and contacted more frequently by telephone to review and adjust their treatment; people in the conventional treatment group were seen and examined every 3 months. [6] The additional RCT, which did not use HbA1c as a primary outcome, found that, compared with conventional treatment, intensive treatment significantly reduced glycated haemoglobin (1 RCT, 1441 people, mean age 27 ± 7 years: median of all quarterly HbA1 values for year 9 of the study: 7% with intensive treatment regimens v 9% with conventional treatment; P less than 0.001). [6] The RCT found no significant difference in quality of life between intensive and conventional treatment programmes as assessed by the Diabetes Quality of Life Measure (DQOL), the Symptom Checklist-90R, the Medical Outcome Study 36 Item Short Form Survey (SF-36), and intercurrent psychosocial events. [8]

Adolescents:

We found no systematic review or RCTs for the outcomes of interest evaluating the effects of interventive treatment programmes with an education component in adolescents with type 1 diabetes.

Harms:

Adults:

The RCT identified by the review found that, compared with control treatment, a significantly higher proportion of people receiving intensive treatment experienced at least one hypoglycaemic episode at 3- and 5-year follow-up (1 RCT, 102 people, mean age 31 ± 7.4 years, attending an outpatient clinic; proportion of people experiencing at least 1 hypoglycaemic episode at 3 years: 57% with intensive treatment v 23% with controls; P less than 0.01; at 5 years: 77% with intensive treatment v 56% with controls; P less than 0.05; at 10 years: 86% with intensive treatment v 73% with controls; P value and absolute numbers not reported). [9] This RCT also reported on the proportion of people experiencing diabetic ketoacidosis (at 7.5 years: 1 episode of diabetic ketoacidosis with intensive treatment v 2 episodes with control; at 10 years: 1 episode with intensive treatment v 4 episodes with control; P values not reported). No data on mortality were reported. [9] The additional RCT found an increased incidence of severe hypoglycaemia with intensive treatment compared with conventional treatment (1 RCT, 1441 people, mean age 27 ± 7 years; 62 hypoglycaemic episodes in which assistance was required/100 patient-years with intensive treatment v 19 hypoglycaemic episodes/100 patient-years with control treatment; P less than 0.001). [6] The RCT found no significant difference between intensive and conventional treatment in diabetic ketoacidosis (2.0 episodes/100 patient-years with intensive treatment v 1.8 episodes/100 patient-years with conventional treatment; P greater than 0.7). It also found similar rates of all-cause mortality (7 deaths with intensive treatment v 4 deaths with conventional treatment; P value not reported). [6] Over a 9-year study period, the RCT found an excess weight gain of 4.75 kg with intensive treatment compared with conventional treatment, with about half the excess weight gain occurring in the first year (3.3 kg weight gain with intensive treatment v 1.2 kg weight gain with control treatment; P less than 0.0001). [10] We also found a second systematic review (search date 1995, 14 RCTs) which included the additional RCT above (1028 adults with type 1 diabetes randomised to intensive treatment and 1039 to conventional treatment), which conducted meta-analyses of adverse effects of intensive treatment in people with type 1 diabetes. [11] The systematic review found that, compared with conventional treatment, intensive treatment significantly increased the risk of hypoglycaemia, and of diabetic ketoacidosis (hypoglycaemia: 14 RCTs, 2067 people, combined OR for hypoglycaemia 2.99, 95% CI 2.45 to 3.64; P less than 0.0001; [11] diabetic ketoacidosis: 14 RCTs, 2067 people, combined OR 1.74, 95% CI 1.27 to 2.38; P = 0.0003). [11] The review found a higher risk of diabetic

ketoacidosis with intensive treatment involving insulin pumps compared with conventional treatment (8 RCTs, 311 people, OR 7.20, 95% CI 2.95 to 17.58; P less than 0.0001). However, it found no significant difference between intensive treatment involving multiple insulin injection compared with conventional treatment (1 RCT, 102 people, plus 3 RCTs, 148 people, where no episodes of diabetic ketoacidosis occurred, OR 1.13, 95% CI 0.15 to 8.35; P = 0.09), and no significant difference between intensive treatment where a choice was offered between insulin pumps and multiple insulin injections compared with conventional treatment (3 RCTs, 1511 people, OR 1.28, 95% CI 0.90 to 1.83; P = 0.17). [11] The systematic review found no significant difference in all-cause mortality between intensive treatment and conventional treatment (14 RCTs, 2067 people, OR 1.40, 95% CI 0.65 to 3.02; P = 0.39), but found a significant increase in mortality that was potentially associated with acute complications of intensive treatment (7 deaths with intensive treatment *v* 0 deaths with conventional treatment [5 deaths attributed to diabetic ketoacidosis, and 2 sudden deaths in young people], OR not reported; P = 0.007). [11] We found no systematic review or RCTs reporting on the effects of intensive treatment programmes on fluid retention.

Adolescents:
We found no systematic review or RCTs in adolescents for the clinical outcomes of interest.

Comment: **Clinical guide:**
The additional RCT (Diabetes Control and Complications Trial [DCCT]) provided convincing evidence of the benefits of intensive insulin treatment in improving glycaemic control, although the intervention group also received frequent follow-up and blood glucose monitoring — meaning that improvements in glycaemic control cannot be attributed solely to the effects of intensified insulin treatment. [6] The results, which represent a large investment of time and resources in a secondary-care setting, may not be reproducible outside the study setting, or in primary care. Most intensive interventions to improve glycaemic control are likely to involve modification of treatment, as well as an educational programme and training in self-management. However, better glycaemic control is associated with higher rates of hypoglycaemia, which may not be acceptable to some people with type 1 diabetes — although the DCCT did not find any difference in quality of life for intensively treated people compared with those receiving conventional treatment. Recent data from the observational Epidemiology of Diabetes Interventions and Complications study (EDIC), a follow-up study of the DCCT cohort, suggest that intensive diabetes treatment has long-term beneficial effects on the risk of CVD in patients with type 1 diabetes. [12] At the end of the DCCT RCT, the conventional treatment group was offered intensive treatment, and all participants returned to their own healthcare providers for diabetes care. During the mean 17 years of follow-up, the EDIC study found that intensive treatment reduced the risk of any CVD event by 42%, and the risk of non-fatal MI, stroke, or death from CVD by 57%. [12] Data from the same follow-up study found that, 6.5 years after DCCT, the former intensive group of DCCT had a significantly lower prevalence of neuropathy compared with the conventional group, based on a positive questionnaire (neuropathy assessed by Michigan Neuropathy Screening Instrument [MNSI]:1.8% with intensive *v* 4.7% with conventional; P = 0.003) or based on clinical examination (18% with intensive v 28% with conventional; P less than 0.0001). [13] Further studies have found a 59% reduction in the odds for development of new cases of microalbuminuria after 7–8 years in people assigned to the intensive arm of DCCT. [14] The DCCT is widely accepted as the "gold standard" RCT demonstrating that tight glycaemic control is of long-term benefit in people with type 1 diabetes. The main adverse impact of tight glycaemic control in the DCCT was a threefold increase in severe hypoglycaemia; but it is noteworthy that there was not a formal structured patient-education programme embedded in the DCCT, and that insulins used in MDI or CSII in the intensively treated patients were human insulins rather than analogue insulins. One of the main challenges of contemporary diabetes care is supporting people to achieve tight glycaemic control comparable to that achieved in the DCCT without increased hypoglycaemia, and this invariably involves the use of both structured patient education and analogue insulins, as well as consideration of CSII using a rapid-acting insulin analogue.

OPTION	EDUCATIONAL INTERVENTIONS

Glycaemic control
Compared with usual care/waiting list control in adults Immediate insulin dose adjustment training to enable dietary freedom (Dose Adjustment for Normal Eating [DAFNE] training) may be more effective at improving HbA1c levels at 6 months, and may maintain the improvement at 1 year (low-quality evidence).

Compared with control in adolescents Educational interventions may be more effective at marginally reducing glycated haemoglobin levels, although differences between groups did not reach significance (very low-quality evidence).

Quality of life

Compared with usual care/waiting list control in adults Immediate insulin dose adjustment training to enable dietary freedom (DAFNE training) may be more effective at improving diabetes-dependent quality of life at 6 months which is maintained at 1 year (low-quality evidence).

Compared with control in adolescents Educational interventions may be more effective at improving psychosocial outcomes including quality of life (very low-quality evidence).

Adverse effects
Compared with usual care/waiting list control in adults We don't know whether immediate insulin dose adjustment training to enable dietary freedom (DAFNE training) is more effective at reducing the frequency of perceived hypoglycaemia scores at 6 months (low-quality evidence).

Note
We found no clinically important results about the effects of group compared with individual educational interventions or secondary-care compared with primary-care educational interventions in adults with type 1 diabetes for the outcomes of interest. We found no direct information evaluating a specific type of education or using HbA1c as the only method for measuring glycaemic control in adolescents, or about the effects of education in adolescents with type 1 diabetes on the incidence of hypoglycaemia, diabetic ketoacidosis, neuropsychological impairment, weight gain, or fluid retention.

For GRADE evaluation of interventions for diabetes: glycaemic control in type 1, see table, p 12 .

Benefits:

Adults:

We found one systematic review (search date 2002), [7] which identified one RCT [16] and one subsequent RCT of education for individuals. [15] The RCT identified by the review found no significant difference in HbA1c levels at 18 months between education in self-monitoring of blood glucose, self-management education, or usual care (1 RCT, 37 adults, aged over 17 years, attending an outpatient clinic; mean reduction in HbA1c: 2.1% with education plus blood glucose self-monitoring *v* 2.0% with blood glucose self-monitoring alone *v* 2.0% with education alone *v* 0.8% with usual care; reported as "did not differ significantly between any of the groups", P value not provided). The RCT was incompletely reported, and may have been underpowered to detect clinically important differences. [16] The subsequent RCT compared immediate insulin dose adjustment training to enable dietary freedom ([DAFNE training) versus a waiting list control group attending insulin dose adjustment training 6 months later. [15] DAFNE training consisted of a 5-day training course providing people with the skills to match insulin dose to desired carbohydrate intake on a meal-by-meal basis. The RCT found that, compared with delayed training in insulin dose adjustment to enable dietary freedom, immediate insulin dose adjustment training significantly improved HbA1c levels and led to a small improvement in diabetes-dependent quality of life at 6 months, and that the improvement was maintained at 1 year (1 RCT, 169 adults with type 1 diabetes and moderate or poor glycaemic control defined as HbA1c 7.5–12%, mean age 40 years; improvement in HbA1c at 6 months: mean difference between groups 1.0%, 95% CI 0.5% to 1.4%; P less than 0.0001; improvement in HbA1c at 12 months: mean difference between groups 0.5%, 95% CI 0.2% to 0.9%; P = 0.001; mean difference between groups in Diabetes Quality Of Life scale at 6 months: 0.4, 95% CI −0.1 to + 0.9; P less than 0.01; at 12 months: quantitative values not reported; on the Diabetes Quality of Life scale, possible scores range from −9 = maximum negative impact of diabetes to +9 = maximum positive impact of diabetes). [15] We found no systematic review or RCTs assessing group education or comparing group education versus individual education, or secondary versus primary care-based education in adults with type 1 diabetes for the outcomes of interest.

Adolescents:

We found one systematic review (search date 1999), which evaluated the effects of different educational and psychosocial interventions in adolescents with type 1 diabetes, and included studies using different measurements for glycated haemoglobin levels and quality of life. [17] Most of the RCTs identified by this systematic review were small studies, lacking sufficient power to detect small to medium effect sizes. They were characterised by a wide variety of interventions and a lack of standardised or validated outcome measures. The control groups in the analysis included usual care, no intervention, an intensive management group without coping skills training (compared with intensive management group with skills training), and a game to play with no health message (compared with a game to play with a diabetes health message). The authors of this review conducted meta-analyses using effect sizes giving a pure number free of the original measurement unit (see comment). The authors stated that, in the behavioural sciences, effect sizes of about 0.2 would be considered small, 0.5 to be medium, and those greater than 0.8 to be large. The review reported psychosocial outcomes which included quality of life, but also other outcome measures including self-efficacy for diabetes, measures of family climate or conflict, and diabetes-specific stress. The review found that, compared with controls, educational interventions produced a small improvement in psychosocial outcomes (search date 1999; 8 RCTs, data on total number of people and age range not available; mean effect size 0.37, 95% CI 0.19 to 0.55). The review also found that, compared with controls, educational interventions reduced glycated haemoglobin (12 RCTs,

573 adolescents, mean age range 9.0–14.5 years; mean effect size +0.33, 95% CI –0.04 to +0.70, equivalent to a reduction in HbA1c of 0.6%; P value not reported). [17] There was significant statistical heterogeneity between included RCTs. A sensitivity analysis removing 2 large RCTs found a smaller effect size (mean effect size +0.08, 95% CI –0.10 to +0.26). We found no systematic review or RCTs of other clinical outcomes of interest in adolescents with type 1 diabetes.

Harms:

Adults:

The RCT identified by the systematic review [7] did not report any data on the incidence of hypoglycaemia, diabetic ketoacidosis, or all-cause mortality for education in self-monitoring of blood glucose, self-management education, or usual care. [16] The additional RCT comparing immediate insulin dose adjustment training to enable dietary freedom (DAFNE training) versus a waiting list control group attending insulin dose adjustment training 6 months later found no significant difference between the two groups in the perceived frequency of hypoglycaemia (1 RCT, 169 adults with type 1 diabetes and moderate or poor glycaemic control defined as HbA1c 7.5–12.0%, mean age 40 years; mean difference in perceived hypoglycaemia score –0.23, 95% CI –0.68 to +0.21; P = 0.31, on a scale of 0–6, where higher scores indicate a higher perceived frequency of hypoglycaemia). [15] This RCT did not report on other outcomes of interest. We found one further follow-up of an RCT of a cohort of 636 people who had paticipated in a 5-day structured inpatient diabetes education programme, which found a significant reduction in HbA1c and risks of severe hypoglycaemic episodes after 6 years compared with baseline (baseline to 6 years: mean HbA1c, 8.3% to 7.6%, P less than 0.001; severe hypoglycaemia, 0.28 cases/person/year to 0.17 cases/person/year, P less than 0.05). [18]

Adolescents:

The systematic review gave no information on adverse effects. [17]

Comment:

The review in adolescents calculated effect size according to the following formula: (difference between group means at follow up) - (difference between group means at baseline) / pooled standard deviation at baseline. [17] Given the nature of type 1 diabetes, and the central importance of self-management of the condition, all people with type 1 diabetes will have received some education at diagnosis. Most studies of the effects of education will therefore be examining the impact of subsequent educational interventions.

Clinical guide:

Adolescents: Although, in theory, the complex changes that occur in adolescence might best be addressed through multiple-intervention programmes that combine an educational element with behavioural training, psychosocial support, and intensification of treatment, in practice it may be difficult to engage some adolescents in such programmes. Adolescents are generally acknowledged to have different educational needs to adults. Adolescence has also been shown to be associated with a worsening of glycaemic control, and with the onset and progression of complications of diabetes. Although some of this deterioration may be due to the physiological changes of puberty, some is undoubtedly due to changes in self-care behaviour. [17] Educational interventions seem to have the potential to improve outcomes in adolescents, but there is little evidence on which to base recommendations about specific educational approaches in terms of their content or setting. There are no RCTs comparing various structured education models. **General:** Structured patient-education programmes are pivotal to achieving tight glycaemic control with an acceptable amount of hypoglycaemia. However, there is a dearth of high-quality published studies, and all the RCTs cited are based upon the Diabetes Teaching and Training Programme which was developed in Düsseldorf (including DAFNE). These programmes are characterised by a set curriculum, a trained healthcare delivery team, and adult learning principles, with a robust quality assurance, including educator peer review and audit. The curriculum is based on carbohydrate counting, and on a basal bolus insulin regimen. At present, there is no uniform follow-up programme after attendance on a DAFNE course, and it would be helpful to have an RCT looking at the impact of structured DAFNE follow-up. The follow-up of an RCT suggested some slippage in glycaemic control by 6 years, [18] and it is likely that a skills-maintenance programme is required following initial attendance on a DAFNE course. Another area worthy of further investigation is the role of both DAFNE and CSII in combination, and at least one such RCT has been proposed. In the UK, the Department of Health has recommended that every Primary Care Trust offers structured education for people with type

1 diabetes. Department of Health and NICE guidelines mention that the DAFNE may be a suitable structured education model. [19] [20]

| QUESTION | What are the effects of different insulin regimens on glycaemic control in adults and adolescents with type 1 diabetes? |

| OPTION | DIFFERENT FREQUENCIES OF BLOOD GLUCOSE SELF-MONITORING |

We found no direct information specifically evaluating the effects of frequency of blood glucose self-monitoring in adults or adolescents with type 1 diabetes for the outcomes of rate of: rise of glycated haemoglobin (measured as HbA1c), quality of life, incidence of and mortality from hypoglycaemia or diabetic ketoacidosis, weight gain, fluid retention, neuropsychological impairment, or all-cause mortality.

For GRADE evaluation of interventions for diabetes: glycaemic control in type 1, see table, p 12 .

Benefits:

Adults:
We found no systematic review or RCTs specifically evaluating the effects of frequency of blood glucose self-monitoring in adults with type 1 diabetes for the outcomes of interest.

Adolescents:
We found no systematic review or RCTs specifically evaluating the effects of frequency of blood glucose self-monitoring in adolescents with type 1 diabetes for the outcomes of clinical interest.

Harms:

Adults:
We found no systematic review or RCTs specifically evaluating the effects of frequency of blood glucose self-monitoring in adults with type 1 diabetes for the outcomes of interest.

Adolescents:
We found no systematic review or RCTs specifically evaluating the effects of frequency of blood glucose self-monitoring in adolescents with type 1 diabetes for the outcomes of interest.

Comment:

Clinical guide:
Adults: One RCT (the Diabetes Control and Complications Trial see benefits of intensive treatment programmes, p 3) and insulin structure self-management programme (including DAFNE) has established the effectiveness of frequent blood glucose monitoring (4 tests/day) as part of an intensive package of care which included intensive insulin treatment, the self-adjustment of treatment in line with preset blood glucose targets, and monthly clinic visits with telephone review between visits. It did not aim to assess the effectiveness of intensive blood glucose monitoring in isolation. Although regular self-monitoring of blood glucose is recommended to people with type 1 diabetes, there are no reliable data on which to base advice about optimum frequency of blood glucose self-testing, except in the setting of a structured intensive insulin self-management programme. Although beyond the scope of this review, the best data for blood glucose monitoring are in pregnancy, where studies have shown significant benefits in glycaemic control in people who monitor blood glucose. **Adolescents:** Maintaining blood glucose levels as close as possible to the normal range has been shown to delay or reduce the onset of long-term complications of diabetes in adults. And frequent blood glucose monitoring, in conjunction with other elements of an intensive treatment programme, has been shown to improve glycaemic control. [6] However, it is recognised that during adolescence metabolic control typically worsens as young people start to take responsibility for managing their diabetes. Frequent blood glucose monitoring may not be a priority for young people developing a more independent and less structured lifestyle, and wanting to fit in with their peer group. Currently, there is little good evidence on which to base advice to adolescents about the optimum frequency of blood glucose self-monitoring. **General:** There are robust data that blood glucose self-monitoring confers benefit in terms of improvement in HbA1c levels in people with type 1 diabetes. Self-monitoring of blood glucose is an essential component of the improved glucose control seen in the landmark DCCT study, and indeed in structured education programmes such as those based around the Structured Teaching and Training Programme (STTP), and the UK version, the DAFNE programme. It is recognised that flexible insulin regimes would be extremely difficult to manage and adopt without the support of self-monitoring of blood glucose. Regarding the frequency of self-monitoring, there is no evidence for the optimal frequency, but it is important to note that, in implementation of the DCCT, and indeed the insulin management programmes,

frequent testing (around 4 times a day) was required. However, different people will have different needs, and will want to use self-monitoring with different frequencies according to their preference.

OPTION	DIFFERENT FREQUENCIES OF INSULIN ADMINISTRATION (CONTINUOUS SUBCUTANEOUS INSULIN INFUSION COMPARED WITH MULTIPLE DAILY SUBCUTANEOUS INSULIN INJECTIONS)

Glycaemic control
Continuous subcutaneous insulin infusion compared with multiple daily subcutaneous insulin injections Continuous subcutaneous insulin infusion may be modestly more effective at improving glycaemic control in adults with type 1 diabetes (very low-quality evidence).

Quality of life
Continuous subcutaneous insulin infusion compared with multiple daily subcutaneous insulin injections using NPH insulin Continuous subcutaneous insulin infusion may be more effective at improving quality of life in adults with type 1 diabetes (very low-quality evidence).

Note
The risk of ketoacidosis may be higher with continuous subcutaneous insulin infusion. This may be due to pump malfunction, and is more often seen in the older-generation pumps.

For GRADE evaluation of interventions for diabetes: glycaemic control in type 1, see table, p 12 .

Benefits: **Continuous subcutaneous insulin infusion versus multiple daily subcutaneous insulin injections:**
Adults:
We found one systematic review (search date 2004; adults, age range not specified) [21] and one subsequent RCT [22] comparing continuous subcutaneous infusion of insulin (CSII) versus multiple daily subcutaneous insulin injections (MDI). The systematic review did not pool data. [21] It included data from two previous systematic reviews, RCTs subsequent to the included reviews, non-randomised controlled studies, and observational data. We have only reported data from systematic reviews of RCTs or individual RCTs here. One of the reviews included in the systematic review [21] pooled RCT data and found that CSII significantly improved HbA1c level after 4 months compared with MDI (4 RCTs, 142 people, WMD –0.84%; 95% CI: –1.59% to –0.16%). It found no significant difference between groups at 6 months (2 RCTs, 52 people, WMD –0.28%, 95% CI –0.64% to +0.08%). However, RCTs included in the analysis had poor methods, and the RCTs were conducted up to 26 years ago (published from 1982–2000) and included older technologies. The review [21] also included three RCTs published after this analysis. One included RCT (79 people with poor glycaemic control, HbA1c level at least 8.5%, adults, age range not specified) compared CSII versus MDI using neutral protamine hagedorn (NPH) insulin. It found that CSII significantly improved HbA1c at 4 months compared with MDI (HbA1c difference: –0.84%, 95% CI –1.31% to –0.36%; P = 0.002), and significantly improved quality-of-life scores (using SF-36 for general health: +5.9 with CSII *v* –1.2 with MDI; P = 0.048; using SF-36 for mental health: +5.2 with CSII *v* –0.6 with MDI; P = 0.05). [21] The two other included RCTs comparing CSII and MDI using glargine were published only as abstracts. One RCT did not report HbA1c as an outcome. The other RCT (57 people, adults, age range not specified) found no significant difference in HbA1c level at 6 months between CSII and MDI (difference: –0.1%, 95% CI –0.5% to +0.3%). [21] The subsequent RCT (272 people, 6 months' treatment, crossover design, age range 18–65 years) compared CSII versus insulin lispro/NPH-based MDI. [22] It found that CSII significantly improved HbA1c, hypoglycaemic episodes, and quality of life compared with MDI (mean HbA1c: 7.45% with CSII *v* 7.67% with MDI, P less than 0.001; ratio of hypoglycaemia frequencies with MDI compared with CSII: 1.12, 95% CI 1.08 to 1.17 for mild hypoglycaemia and 2.61, 95% CI 1.59 to 4.29 for severe hypoglycaemia; diabetes QoL score: 75 with CSII *v* 71 with MDI, P less than 0.001). [22] The results were post-crossover, and the follow-up rate was 82% (223/272).

Adolescents:
We found no systematic review or RCTs.

Harms: **Continuous subcutaneous insulin infusion versus multiple daily subcutaneous insulin injections:**
Adults:
The systematic review included data from previous systematic reviews, RCTs subsequent to the reviews, and non-randomised controlled studies and observational data. [21] Based on a general overview of included studies, it reported that RCTs "do not indicate any difference in the incidence of severe hypoglycemic episodes" in people treated with continuous subcutaneous insulin infusion (CSII) compared with multiple daily injections (MDI), but non-randomised observational studies reported fewer severe hypoglycemic episodes in pump-treated people. [21] The review stated that

this might be explained in non-randomised studies, where pump treatment is proposed to those who might benefit most from it. Regarding incidence of ketoacidosis, the review included data from three earlier reviews. [21] One of these reviews stated that included studies found "no difference" in the incidence of ketoacidotic episodes between pump-treated people and those treated by multiple injections, and that there was a greater number of such episodes in older studies. This conclusion was similar to that of another included review. Another included review pooled data from RCTs to analyse risks from intensive compared with conventional treatment. [11] It found that, if intensive treatment involved insulin pumps providing continuous insulin infusion, there was a a significantly higher risk of diabetic ketoacidosis than with conventional treatment (8 RCTs, 311 people, OR 7.20, 95% CI 2.95 to 17.58; P less than 0.0001). However, it found no significant difference in diabetic keoacicdosis between intensive treatment involving multiple insulin injection and conventional treatment (1 RCT, 102 people, plus 3 RCTs, 148 people, where no episodes of diabetic ketoacidosis occurred, OR 1.13, 95% CI 0.15 to 8.35; P = 0.09). [11] All but one of the RCTs involving pump treatment were done before 1990. [21] Overall, the review suggested that, while there was no significant difference, most of the trials noted a higher absolute number of ketoacidotic episodes with the pump than with MDI, and that ketoacidotic episodes were more frequent with the first generations of pumps, but that they occurred less often in the more recent studies. The subsequent RCT reported a total of 33 serious adverse effects in 23 people receiving CSII and a total of 58 serious adverse effects in 30 people receiving MDI (further numerical details and statistical analysis between groups not reported). [22] It reported that most adverse effects (70%) were related to metabolic problems, including severe hypoglycaemia and diabetic ketoacidosis. It reported that ketoacidosis occurred very rarely (total frequency 0.03 events/patient-year). [22]

Adolescents:
We found no RCTs.

Comment:

Clinical guide:

There are potential short-term disadvantages to intensive insulin treatment (whether achieved by continuous subcutaneous insulin infusion or multiple daily subcutaneous insulin injections) in terms of the need for multiple injections, an increased risk of hypoglycaemia, and, in the case of continuous subcutaneous insulin infusion (CSII), the potential hazards and inconvenience associated with the pump itself (diabetic ketoacidosis due to disconnection or malfunction of the pump, infection, siting of the device, etc). The available evidence suggests that intensive treatment does not significantly impair quality of life in the short- to medium-term, but data about longer-term and less common outcomes, especially with regard to CSII, are lacking. Increasingly, CSII has been adopted worldwide to achieve tight glycaemic control in type 1 diabetes where recurrent and disabling hypoglycaemia has limited tight glycaemic control with multiple daily injections (MDI). This approach will be suitable for people who need a variable rate of basal insulin. This is in keeping with the observational studies where clinicians have selected people whom they believe will particularly benefit from CSII, and such studies have reported fewer hypoglycaemic episodes. There is a growing consensus that CSII is particularly beneficial for women planning to become pregnant, as well as for adolescents who may omit injections in an MDI regimen, but who are prepared to insert a cannula for CSII every 3 days and undergo regular blood glucose monitoring. CSII is also an option for people with needle phobia or insulin allergies, but the number of such people is too small for a robust RCT. A key RCT yet to be done would be a comparison of CSII against a formal structured education programme such as DAFNE. However, a structured education programme is required at the initiation of CSII.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Different frequencies of insulin administration (continuous subcutaneous insulin infusion compared with multiple daily subcutaneous insulin injections) Option restructured to include adults and adolescents. One systematic review [21] and one subsequent RCT [22] added; benefits and harms data enhanced. 'Continuous subcutaneous insulin infusion (compared with multiple daily subcutaneous insulin injections)' categorised as Trade-off between benefits and harms.

Educational interventions Option restructured to include both adults and adolescents. One previously reported RCT in another option now reported in this option, [15] and long-term follow-up data from another RCT added to the harms section. [18] 'Educational interventions (compared with controls)' categorised as Likely to be beneficial.

Intensive treatment programmes Option restructured to include both adults and adolescents. Existing evidence re-evaluated. One previously included RCT in this option [15] omitted from this option and now reported under the

educational interventions option. 'Intensive treatment programmes (compared with conventional treatment programmes)' categorised as Likely to be beneficial.

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TABLE	GRADE evaluation of interventions for diabetes: glycaemic control in type 1

Important outcomes — Glycaemic control, quality of life, mortality, adverse effects

Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of intensive treatment programmes and educational interventions in adults and adolescents with type 1 diabetes?									
2 (1543) [6] [9]	Glycaemic control	Intensive v conventional treatment programmes or control in adults	4	−1	0	−2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for uncertainty about applicability of results, for not measuring HbA1 as a primary outcome in one RCT, and for inclusion of other interventions in one intensive treatment programme
1 (1441) [8]	Quality of life	Intensive v conventional treatment programmes or control in adults	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
15 (2169) [6] [9] [11]	Adverse effects	Intensive v conventional treatment programmes or control in adults	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
14 (2067) [11]	Mortality	Intensive v conventional treatment programmesor control in adults	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (206) [16] [15]	Glycaemic control	Educational interventions v usual care/controls in adults	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (169) [15]	Quality of life	Educational interventions v usual care/controls in adults	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and sparse data
12 (573) [17]	Glycaemic control	Educational interventions v usual care/controls in adolescents	4	−1	0	−2	0	Very low	Quality points deducted for incomplete reporting of results. Directness points deducted for wide range (heterogeneity) of interventions and for lack of standardised or validated outcome measures
8 (?) [17]	Quality of life	Educational interventions v usual care/controls in adolescents	4	−1	0	−2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for wide range of interventions and for lack of standardised or validated outcome measures and use of a composite outcome measure
What are the effects of different insulin regimens on glycaemic control in adults and adolescents with type 1 diabetes?									
9 (602) [21] [22]	Glycaemic control	Continuous subcutaneous insulin infusion v multiple daily subcutaneous insulin injections	4	−3	−1	−1	0	Very low	Quality points deducted for incomplete reporting of results and for poor methodologies. Consistency point deducted for conflicting results. Directness points deducted for assessing different outcomes
2 (351) [21] [22]	Quality of life	Continuous subcutaneous insulin infusion v multiple daily subcutaneous insulin injections	4	−3	0	0	0	Very low	Quality points deducted for incomplete reporting of results and for poor methodologies

Type of evidence: 4 = RCT; 2 = Observational
Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio